COMBINED TOPICAL AND SYSTEMIC METHOD OF ADMINISTRATION OF CYCLOSPORINE

BACKGROUND OF THE INVENTION

Cyclosporine (CsA), a selective immunosuppressant and a potent anti-inflammatory agent, has demonstrated great clinical success in inhibiting T-cell mediated immune processes such as allograft rejection, graft-versus-host disease, and autoimmune disease when administered systemically. (See, e.g., A. D. Hess al., *Transpl. Proc.* 20: 29 (1988).) As to the latter, systemic CsA has been proven efficacious for treating psoriasis autoimmune disorder of the skin. (See, e.g., C. N. Ellis, et al., *JAMA* 256: 3110 (1986).) However, the induction of tissue site and focal responding immunocytes could result in surprisingly greater efficacy, and could have significant immunologic and clinical ramifications.

As an example of the aforementioned ramifications, within the specialty of dermatology, it would be desirable to treat putative autoimmune conditions and related diseases of the skin, including, for example, eczema, contact hypersensitivity, alopecia areata and psoriasis. Few if any models for testing the disease mechanism and the efficacy of various treatment modalities have been available in this field, however. Moreover, due to the variability of expression of most skin conditions, and the inherent differences between epidermal tissues in various locations on the body, a single treatment methodology or pharmaceutical composition is rarely effective for all disease conditions presented.

A basic understanding of the immune response involved will facilitate the understanding and appreciation of the present invention. T-cell mediated immune events play an important role in eliciting allograft rejection and other inflammatory reactions. The immunological cascade that follows alloengraftment includes: (1) recognition of antigen; (2) lymphocyte activation; (3) development of specific cellular and molecular lines of communication between responding immunocytes via lymphokine release and induced expression of major histocompatibility complex ("MHC") antigens; and (4) mononuclear inflammatory cell infiltration into the target tissue which leads to eventual graft destruction (rejection). Systemic administration of CsA, a novel fungal metabolite, is well known to block this inflammatory cascade and to facilitate permanent allograft acceptance (actively-acquired immunological tolerance) in various experimental animal models, probably by inhibitory effects upon T-helper cells with sparing of cell expression. (See, e.g., A. D. Hess, et al., *Transpl. Proc.* 29 (1988).) Cyclosporins have novel immunosuppressive properties compared to conventional agents: they are selective in their mechanism of action, demonstrate superior graft survival times, and are potent anti-inflammatory compounds. Cyclosporins are well-recognized for their powerful ability to permanently alter immune responsiveness, in comparison with conventional agents, so that some degree of selective immunologic tolerance (graft acceptance) can be achieved in various models. Therefore, it would be extremely advantageous and desirable to develop topical formulations of cyclosporins for localized tissue site-specific action.

Conventionally, immunosuppressants have been administered at a systemic level in order to inhibit both cell- and humoral-mediated immune responses. However, the induction of localized site-specific immunosuppression could inhibit the mechanisms which lead to graft rejection and similar inflammatory immune processes operative in autoimmune and putative autoimmune disorders. Yet, a tissue site-specific immunosuppressive mechanism has not been conclusively demonstrated by local application of the cyclosporins.

More recently, the fungal metabolites known as cyclosporins, and particularly Cyclosporine A (CsA), have been established as the principal immunosuppressants in solid organ transplantations. The systemic use of cyclosporin prolongs the survival of experimental and clinical allografts, but continuing immunosuppressive therapy is generally necessary.

Yet, the long-term side effects of systemic administration of cyclosporins are of major concern. The related complications of nephrotoxicity and hepatotoxicity (i.e., kidney and liver damage), as well as an increase in infections, are a significant problem and may thus render treatment with cyclosporins inappropriate for certain patients, such as those who have been severely burned, or for those with skin conditions that are not life-threatening, such as psoriasis. One method for achieving indefinite survival of the graft or prolonged anti-inflammatory effects with CsA and for reducing its potentially toxic systemic side effects involves the localization of CsA in the target tissue.

For the purposes of clarity and easier comprehension, the terms "CsA", "Cyclosporine A" and "cyclosporine" may be considered interchangeable with the term "cyclosporin(s)" throughout this disclosure. While CsA is the cyclosporin typically used in most pharmaceutical preparations, the scope of this invention is not limited to this one type of cyclosporin.

Local inhibition of the rejection response with CsA has demonstrated mixed results. Perfusion of kidney allografts with CsA prior to transplantation did produce enhancement of tissue survival; however, prior, minimal systemic azathioprine immunosuppression was required. See, e.g., L. H. Toledo-Pereyra, et al., *Transplantation* 33: 330 (1982). Likewise, infusion of low-dose CsA into the ligated thoracic duct provided only a mild enhancement of rat kidney allograft survival. Delayed type hypersensitivity has been effectively inhibited in animals and man with topically-applied CsA (see, e.g., R. D. Aldridge, et al., *Clin. Exp. Immunol.* 59: 23, 1985), as has cornea allograft rejection. The topical application of CsA has also been shown to be effective in treating alopecia areata and contact hypersensitivity in humans, yet it appears to have no effect on psoriasis. Studies using topically-applied CsA demonstrated prolonged survival of rat skin allografts; see, e.g., C. S. Lai, et al., *Transplantation* 44: 83, 1987; X.F. Zhao, et al., *Transplant. Proc.* 20: 670 (1988). However, one such study concluded that most of the enhancement observed with local CsA treatment was due to the animals, ingestion of CsA from the treated area. See Zhao, supra. When means were taken to prevent the animals from ingesting CsA from the grafts, the investigators found that CsA blood levels were suboptimal (below 100 ng/ml) and negligible enhancement of skin allograft survival was seen. It has also been postulated that autoimmune disorders of the skin could benefit from transdermal (i.e., localized) treatment with CsA.

Thus, there is a need for topical and local formulations of cyclosporins, and a method for utilizing same, in the prevention of localized tissue site-specific inflammatory immune reactions. An example includes prevention of skin allograft rejection at a local level, but this